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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,954	11/30/2001	Harlan W. Waksal	11245/46605	3116

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Kenyon & Kenyon
One Broadway
New York, NY 10004

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,954	WAKSAL, HARLAN W.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-70* is/are pending in the application.

4a) Of the above claim(s) *45-47,56-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-44,48-55 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Objections

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). In this case, originally claims 1-33 were presented, and then canceled by amendment on 1/18/2002.

Misnumbered claims 36-72 have been renumbered as 34-70.

Election/Restrictions

2. Applicant's election without traverse of species A, where the epidermal growth factor antagonist is an anti-EGFR antibody, in the reply filed on 12/12/2005 is acknowledged.

3. Claims 34-70 are pending. Claims 45-47 and 56-71, drawn to non-elected inventions, are withdrawn from consideration. Claims 34-44, 48-55 and 70 are examined on the merits, and to the extent the claims read on methods comprising the administration of an anti-EGFR antibody.

Claim Rejections - 35 USC § 112

4. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification lacks descriptive support for the claimed inventions.

In the case of claim 40, the invention comprises a method for inhibiting the growth of a refractory tumor comprising administering an EGFR antagonist that is an anti-EGFR antibody, wherein the administration is oral. Neither the originally filed claims nor the specification describe a formulation comprising an anti-EGFR antibody that may be administered orally. The specification provides a general contemplation of administering chemotherapeutic agents either parenterally or enterally, but this is insufficient support for a method comprising the oral administration of an anti-EGFR antibody. Therefore, it does not appear that applicant was in possession of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 34-39, 41-44, 49-52 and 70 are rejected under 35 U.S.C. 102(a) as being anticipated by Perez-Soler (Perez-Soler, et al, 34th Annual Meeting of the American Society of Clinical Oncology, 17: 393, May 16, 1998) as evidenced by Herbst (Herbst, R.S. et al, Expert Opin. Biol. Ther. (2001) 1(4): 719-732).

The claims are drawn to methods of inhibiting the growth of a refractory tumor that has failed or been resistant to treatment comprising administering to a human an epidermal growth factor receptor antagonist that is an anti-EGFR antibody, wherein the administration is effective to inhibit the growth of the refractory tumor.

It is noted that the claims fail to recite that the human to be treated has a refractory tumor.

Perez-Soler teaches a method comprising the administration of chimeric 225 antibody (C225), which is an antibody that binds EGFR externally, to patients having recurrent head and neck cancer. Recurrent head and neck cancer falls within the scope of a refractory tumor (failed or been resistant to treatment). The dose of antibody is 100mg/m^2. Two transient minor responses were observed (falls within the scope of effective to inhibit the growth of the refractory tumor). IHC analysis of activated EGFR showed minimal expression post-therapy suggesting complete functional inhibition of EGFR, and functional saturation (reads on inhibiting stimulation of EGFR by ligand, inhibiting binding of EGFR to its ligand, inhibiting EGFR tyrosine kinase activity, inhibiting EGFR phosphorylation). It is standard in the art to administer antibodies intravenously. Head and neck cancers appear to be squamous cell carcinoma (see Herbst, page 719, 1st paragraph). Cisplatin was also administered (reads on comprising administering an adjuvant). Thus, Perez-Soler teaches the claimed methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 34-36, 39, 41-44, 48-51, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang (Yang, X.-D., et al, Cancer Res. 59: 1236-1243, 1999, March 15) in view of Prewett (Prewett, M. et al, Journal of Immunotherapy, 19(6): 419-427, 1997).

Yang teaches a completely human anti-EGFR antibody (E7.6.3). Yang teaches the administration of the antibody to mice having human tumor xenografts of A431 cells or of MDA-MB-468 cells breast cancer cells. Adminstration is intraperitoneal, , subcutaneous, intravenous or intramuscular (i.p, s.c., i.v., or i.m.; see page 1240, 2nd paragraph). The E7.6.3 Mab blocks EGF-triggered EGFR tyrosine kinase phosphorylation (page 1238, 1st column, 4th full paragraph), and blocks EGF activation of EGFR (page 1238-1239, bridging paragraph). The antibody binds the EGFR externally. E7.6.3 blocks binding of EGF to EGFR (page 1238, 1st column, first full paragraph, see also page 1242-1243, bridging paragraph).

Yang fails to teach administration to a human, and that administration would be effective to inhibit the growth of a refractory tumor. However, Prewett teaches that autocrine stimulation of EGFR by TGF-α may have relevance to the refractory nature of prostatic carcinoma to chemotherapy and suggests that antibodies to EGFR may provide a therapeutic intervention

(page 419-420 bridging paragraph). Prewett further teaches that A431 tumor xenografts are autocrine for production of TGF-α (page 420, 2nd full paragraph). Therefore, the A431 xenograft model used by Yang appears to be a good model for a refractory tumor.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the fully human anti-EGFR antibody of Yang (E7.6.3) for the treatment of human patients having refractory tumors, because Yang demonstrates that this antibody fully eradicates A431 tumor xenograft tumors, and because Yang demonstrates that the E7.6.3 antibody blocks the binding of ligand to the EGFR. One would have had a reasonable expectation of success given the data supplied by Yang demonstrating the ability of the E7.6.3 antibody to totally eradicate the A431 tumor xenograft, which appears to be a good model for a refractory tumor.

7. Claims 34-36, 41-44, 48-51, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein (Goldstein, N.I. et al, Clinical Cancer Research, 1: 1311-1318) in view of Prewett (Prewett, M. et al, Journal of Immunotherapy, 19(6): 419-427, 1997).

Goldstein teaches the administration of a chimeric anti-EGFR antibody (C225) to mice bearing the A431 xenograft tumor. C225 was extremely effective in inhibiting the growth of A431 tumors (page 1314, 1st to 2nd column, bridging paragraph). The C225 antibody competes with the ligand for binding to EGFR and blocks activation of the EGFR (see abstract). The C225 antibody appears to block the function of EGFR (see page 1317, 1st to 2nd column, bridging paragragph) (reads on inhibiting EGFR tyrosine kinase activity and inhibiting EGFR phosphorylation). Goldstein fails to teach administration to a human, and that administration

would be effective to inhibit the growth of a refractory tumor. However, Prewett teaches that autocrine stimulation of EGFR by TGF-α may have relevance to the refractory nature of prostatic carcinoma to chemotherapy and suggests that antibodies to EGFR may provide a therapeutic intervention (page 419-420 bridging paragraph). Prewett further teaches that A431 tumor xenografts are autocrine for production of TGF-α (page 420, 2nd full paragraph). Therefore, the A431 xenograft model used by Yang appears to be a good model for a refractory tumor.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the chimeric anti-EGFR antibody of Goldstein (C225) for the treatment of human patients having refractory tumors, because Goldstein demonstrates that this antibody inhibits the growth of A431 tumor xenograft tumors, and because Goldstein demonstrates that the C225 antibody blocks the binding of ligand to the EGFR. One would have had a reasonable expectation of success given the data supplied by Goldstein demonstrating the ability of the C225 antibody to inhibit the growth and cause complete remission of the A431 tumor xenograft, which appears to be a good model for a refractory tumor.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 34-55 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-56 and 72-87 of copending Application No. 11/018,950. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to methods comprising the administration of an EGFR antagonist, whereas the claims of copending application 11/018,950 are drawn to methods comprising the administration of an EGFR antagonist in combination with a chemotherapeutic agent, which is encompassed by the claims of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
March 6, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER